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Delayed Consequences of Acute Kidney Injury

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Abstract

Acute kidney injury (AKI) is an increasingly common complication of hospitalization and acute illness. Experimental data indicate that AKI may cause permanent kidney damage through tubulointerstitial fibrosis and progressive nephron loss, while also lowering the threshold for subsequent injury. Furthermore, preclinical data suggest that AKI may also cause distant organ dysfunction. The extension of these findings to human studies suggests long-term consequences of AKI including, but not limited to recurrent AKI, progressive kidney disease, elevated blood pressure, cardiovascular events, and mortality. As the number of AKI survivors increases, the need to better understand the mechanisms driving these processes becomes paramount. Optimizing care for AKI survivors will require understanding the short- and long-term risks associated with AKI, identifying patients at highest risk for poor outcomes, and testing interventions that target modifiable risk factors. In this review, we examine the literature describing the association between AKI and long-term outcomes and highlight opportunities for further research and potential intervention.

Keywords

Acute kidney injury (AKI); Chronic kidney disease (CKD); End-stage renal disease (ESRD); Mortality

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Introduction

Acute kidney injury (AKI) is an increasingly common disease that complicates up to 1 in 5 hospitalizations.¹⁻⁸ The conventional belief that AKI is ‘self-limited’ has been challenged by studies showing an association between AKI and progressive kidney disease,⁹⁻¹³ cardiovascular events,¹⁴⁻¹⁶ and short- and long-term mortality.^{1,7,17-20} The combination of population growth, increasing AKI incidence,⁸ and improved short-term survival^{7,21,22} have resulted in an expanding population of AKI survivors at risk for these outcomes. In this review, we will examine literature describing the association between AKI and incident and progressive chronic kidney disease (CKD), end-stage renal disease (ESRD), cardiovascular events, and mortality. We will also discuss processes that may modify the course of disease in the post-AKI period (Figure 1), and future research that will be needed to identify potential interventions and define optimal care.

Incident CKD Following AKI

The traditional belief that AKI survivors often experience full recovery is likely rooted in early clinical observations that young patients with presumed normal baseline kidney function who experienced severe AKI often had a good *clinical* recovery, resuming their occupations and prior functional capacity.^{23,24} However, carefully performed physiologic measurements demonstrated that renal recovery was often incomplete. Using thiosulphate and para-amino hippurate (PAH) clearances, Lowe et al²³ demonstrated that kidney function remained below the lower limit of normal in the majority of patients over a 3-year follow-up period. Using PAH and inulin clearances, Finkenstaedt and Merrill also reported that “clearance values remained below the lower limit of normal in most patients...consistent with permanent renal damage of mild degree.”²⁴ These studies were small, and lacked appropriate controls and measures of baseline kidney function, but indicated that AKI may not truly be ‘self-limited’.

Following these early reports, experiments in animal models of AKI have elucidated potential mechanisms for post-AKI residual kidney impairment including interstitial inflammation, capillary rarefaction, and chronic hypoxia, leading to tubulointerstitial fibrosis and progressive nephron loss.²⁵⁻²⁷ Physiologic derangements that potentially lower the threshold for subsequent injury have also been reported, including hyperfiltration, urinary concentrating defects, impaired sodium-handling, enhanced pressor response, and impaired autoregulation of renal blood flow (Figure 1).^{25,26}

Some evidence suggesting a potential link between AKI and future kidney disease in humans comes from pediatric studies. While adult populations who experience AKI often have ‘reduced renal reserve’ and comorbidities (i.e. diabetes and hypertension) that confound the association between AKI and CKD, the low prevalence of these conditions in the pediatric population supports a link between AKI and future CKD. Mammen et al²⁸ evaluated a pediatric ICU population with AKI for subsequent development of CKD, defined as albuminuria or eGFR <60mL/min/1.73m². The distribution of AKIN Stages 1, 2, and 3 were 35%, 37%, and 28%, respectively. Over a median follow-up period of approximately 1 year, the incidence of CKD was 10% overall, and increased in a graded manner with AKI

severity from 5% to 17%. Additionally, 47% of patients were identified as being at increased risk for future CKD based on hypertension, mildly decreased GFR, or hyperfiltration. In another study by Garg et al,²⁹ 19 children recovering from hemolytic-uremic syndrome (HUS) were compared with a control group of 64 healthy children. At 5-year follow-up, HUS survivors had a higher prevalence of microalbuminuria compared with controls (20% versus 3%) with a relative risk of 6.0. Collectively, these and other pediatric studies^{30,31} suggest a potentially causal role of AKI in future development of CKD, and highlight hypertension and albuminuria as important modifiable factors in the follow-up period. However, the majority of these studies were limited by small sample size and lack of a control population.

Several studies in adults have also demonstrated evidence of an association between hospitalized AKI and future incident CKD (Table 1). Within a large integrated healthcare system in Northern California, Lo et al¹³ evaluated the risk for developing Stage 4 or 5 CKD in patients with baseline eGFR >45 ml/min/1.73m² (including 68% with eGFR>60) who experienced dialysis-requiring AKI and were dialysis-independent 30 days post-discharge. After matching and adjusting for multiple clinical factors, including baseline eGFR, an episode of dialysis-requiring AKI was independently associated with a 28-fold increase in risk for developing Stage 4 or higher CKD over 10,344 person-years of follow-up. While 84% of patients who survived the index hospitalization recovered to become dialysis-independent, they had a substantially increased risk of developing advanced CKD.

The association between less severe AKI and future CKD has also been examined. In 29,388 Veteran patients undergoing cardiac surgery, Ishani et al³² evaluated the relationship between magnitude of acute post-operative serum creatinine increase and the risk for incident CKD (persistent eGFR < 60 mL/min/1.73m²). AKI severity was categorized by a proportional increase in serum creatinine from baseline, defined as class I (1%-24%), class II (25%-49%), class III (50%-99%), or class IV (100%). The investigators observed a graded association between magnitude of post-operative creatinine increase and risk for incident CKD. Risk was greatest 3 months after surgery, with creatinine increase classes I-IV conferring hazard ratios (HRs) of 2.1-6.6. The persistence of these associations at 5 years, though attenuated (HRs 1.5-2.4), provides further evidence linking less severe AKI with future CKD risk.

To evaluate the hypothesis that even reversible AKI may have long-term consequences, Bucaloiu et al³³ studied patients with normal baseline kidney function and without proteinuria who experienced reversible AKI, defined as a return of creatinine to within 90% of baseline within 90 days of AKI, and compared them to matched non-AKI controls. Survivors of AKI had a significantly increased risk of developing incident CKD over a median follow-up time of 3.3 years, with a HR of 1.91. Among patients experiencing AKI, 71% had AKIN Stage I AKI, and the duration was less than 24 hours in 75% of patients, suggesting that even mild, transient AKI predicts risk for future CKD. However, it is unclear whether mild AKI *causes* incident CKD, or whether AKI is simply more likely to occur in patients with higher comorbidity burden and subtle underlying renal abnormalities who are already predisposed to develop CKD.

CKD Progression and ESRD Following AKI in Adults

Given observations that progression to ESRD is frequently non-linear and punctuated by AKI episodes,^{11,34} it is important to consider the potential contribution of AKI to the advanced CKD burden. Multiple studies have demonstrated the association between AKI and progressive CKD and/or ESRD, several of which have been included in Table 2. Ishani et al³² examined CKD progression following cardiac surgery. Progression was assessed using a moving average eGFR and defined by a persistent reduction in eGFR constituting an increase in CKD Stage. The risk of CKD progression was highest 3 months post-operatively with adjusted hazard ratios (aHRs) of 2.5-8.0 depending on the magnitude of post-operative increases in serum creatinine. While misclassification of recovering AKI as progressive CKD in the months after discharge is possible, the persistence of this association at 5 years (aHRs 1.5 - 2.4) support the robustness of these findings.

Wald et al³⁵ examined the risk for chronic dialysis in a population-based study using administrative data in Ontario, Canada. In this study, patients who recovered from dialysis-requiring AKI and survived at least 30 days after discharge were matched with hospitalized patients who did not have AKI. The incidence rate of chronic dialysis was 2.63 per 100 person-years in patients with dialysis-requiring AKI, versus 0.91 per 100 person-years in controls (aHR 3.23) over a median follow-up time of 3 years. An episode of dialysis-requiring AKI was associated with an approximately 2-fold and 15-fold higher risk for developing chronic dialysis in patients with and without underlying CKD, respectively, compared to hospitalized patients without dialysis-requiring AKI.

In a systematic review of 13 cohort studies, Coca et al¹² found that compared to patients without AKI, patients experiencing AKI had higher risk for CKD with a pooled aHR of 8.8.¹² This risk increased in a dose-response fashion with mild, moderate, and severe AKI having aHRs of 2.0, 3.3, and 28.2, respectively. Patients with AKI also had a higher risk for developing ESRD compared to patients without AKI, with a pooled aHR of 3.1.¹² The risk for ESRD also increased in a dose-response manner, with mild, moderate, and severe AKI having aHRs of 2.3, 5.0, and 8.0, respectively, compared to patients without AKI.

The Debate Surrounding Causality

While there is significant data supporting an association between AKI and both development and progression of CKD,³⁶ the issue of causality is often debated due to the observational nature of most of the evidence.³⁷ Several factors, which may lead to spurious or inflated associations, need to be considered. First, residual confounding may be present in these observational studies. Patients who experience AKI are often 'sicker', with higher prevalences of established risk factors for CKD, including diabetes and hypertension. Since these are also known risk factors for AKI, it is possible that AKI merely occurs in patients who are already at highest risk for developing CKD. Secondly, in observational studies which rely on retrospective creatinine values to diagnose the disease state, there is the potential for misclassification of CKD progression as AKI. For example, if baseline creatinine is not accurately defined, worsening CKD may be incorrectly diagnosed as AKI. In this scenario, an erroneous diagnosis of AKI in a patient with worsening CKD would inflate the estimate of the association between AKI and CKD progression. Finally, patients

who experience AKI may have kidney function checked more frequently than those without AKI, differentially increasing the likelihood of being diagnosed with CKD through ascertainment bias in the AKI group.

The ideal study to determine whether AKI is causal in CKD would be a trial randomizing patients to an intervention that causes AKI. Because such a study is not ethical, results from randomized clinical trials where an intervention reduces the incidence of AKI may be informative. In a recent study with patients randomized to ‘off-pump’ or ‘on-pump’ coronary artery bypass graft (CABG) surgery, Garg et al³⁸ observed a 17% reduction in AKI incidence in the group randomized to off-pump surgery. Despite the reduction in AKI, kidney function at one year was not different between groups, supporting the possibility of residual confounding in earlier observational studies. Notably, the majority of patients (62%) in this study had mild AKI, which may not cause substantial CKD or may require longer than one year to manifest. The findings from this study call for reevaluation of whether there is a causal relationship between mild AKI and CKD. However, the biological plausibility provided by animal studies, the graded nature of the association between AKI severity and future CKD risk, and universal clinical experience leave less debate as to how a severe episode of AKI can alter the trajectory of kidney function decline. Well-executed studies such as the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI)—a matched, prospective cohort study including patients with and without AKI, with long-term follow-up—may better characterize the natural history of AKI, refine the precision of effect size estimates, and overcome the ascertainment and confounding concerns from prior studies.³⁹

Recurrent AKI

Recent clinical observations have extended upon experimental data suggesting that AKI is associated with an increased risk for future AKI episodes.^{11,40} Impaired renal reserve and autoregulation as well as the residual effects of acute illness or its therapies may be contributors to AKI risk in this population. In a study of US Veterans with diabetes and normal baseline kidney function, Thakar et al¹¹ examined the relationship between episodes of AKI and progression to stage 4 CKD. Within this cohort, 29% of patients had at least one AKI episode, and of those, 30% had 2 episodes. The majority of the AKI events were mild (88% Stage 1). However, over the median follow-up time of approximately 5 years, Stage 4 CKD occurred in 23.4% of AKI survivors, compared to only 10.4% in hospitalized patients who did not experience AKI. After adjustment for clinical factors including baseline eGFR and proteinuria, patients who experienced any AKI had over a three-fold increased risk for development of Stage 4 CKD, and each *individual* AKI event was associated with a doubling in the risk for progression to Stage 4 CKD.

Siew et al⁴⁰ also demonstrated that patients with hospitalized AKI are at risk for recurrent AKI and re-hospitalization in the 12 months after the index AKI episode. In this study, 49% of AKI survivors were re-hospitalized at least once during the follow-up period, and 25% of patients experienced recurrent AKI. The median time to recurrent AKI was 64 days, highlighting the potential opportunity to identify and intervene on dynamic risk factors in the immediate post-discharge period. This study also evaluated predictors of recurrent AKI,

and found that discharge diagnoses of congestive heart failure, decompensated liver disease, cancer with or without chemotherapy, acute coronary syndrome, and volume depletion during the *index* AKI hospitalization were important inpatient risk factors for recurrent AKI (Figure 2).

These studies demonstrate that recurrent AKI is common and may be a mechanism contributing to long-term loss of kidney function following AKI. Developing strategies to reduce recurrent AKI may be an important pathway to improve long-term outcomes in AKI survivors.

Cardiovascular Outcomes Following AKI

The association between CKD and cardiovascular disease (CVD) is well-documented.^{41,42} However, the correlation between AKI and cardiac morbidity and mortality has not been extensively examined. Preclinical data suggest that AKI can cause distant organ dysfunction in the heart,⁴³ liver,⁴⁴ brain,⁴⁵ and lung.⁴⁶⁻⁴⁸ For example, Kelly demonstrated that renal ischemia-reperfusion injury can have detrimental effects on cardiac function including increased cytokine expression, myocyte apoptosis, and left ventricular dysfunction.⁴³

Several studies in humans have evaluated how AKI in patients with *prevalent* CVD increases the risk for future cardiovascular events. Chawla et al¹⁴ evaluated risk for major cardiac events over a median of 1.4 years within a cohort of Veteran patients with administrative discharge diagnosis codes for AKI and/or myocardial infarction (MI). Patients experiencing MI complicated by AKI had higher incidence of major adverse cardiac events (subsequent MI, stroke, or heart failure) and were nearly two times more likely to be admitted for heart failure (HF) than those experiencing MI without concomitant AKI. It should be noted that severity of cardiac disease was not ascertained in this study. Thus, AKI may have occurred in patients with the most severe coronary disease, who are inherently at highest risk for subsequent cardiac events. In a study that adjusted for severity of cardiac disease, Goldberg et al¹⁵ evaluated a cohort with ST-elevation MI and assessed the association between AKI and future HF admissions. Both severity and duration of AKI conferred increased risk for HF readmission, with aHRs for mild persistent, moderate/severe transient, and moderate/severe persistent AKI of 1.7, 1.7, and 2.0, respectively.

Wu et al¹⁶ examined the risk for future coronary events (nonfatal MI, coronary artery bypass graft, and coronary angiography) among Taiwanese patients with dialysis-requiring AKI who recovered kidney function, compared with matched non-AKI controls. The unadjusted incidence rate of coronary events was 19.8 per 1000 person-years in the AKI group, compared with 10.3 per 1000 person-years in the non-AKI group, with an adjusted hazard ratio of 1.67. Notably, the low rates of recovery of kidney function (30%) and in-hospital mortality (15%) compared to other studies suggest that unrecognized baseline CKD may have been present and could have contributed to the observed cardiovascular risk, independent of AKI.

These studies highlight that AKI may confer risk for future cardiovascular events. Further research in this area focusing on accurate phenotyping of pre-morbid conditions and severity

of CVD, as well as potential mechanisms by which AKI contributes to cardiovascular outcomes will be required to validate these findings.

Blood Pressure Elevation Following AKI

One important mechanism by which AKI may increase the risk for CKD and CVD is by increasing blood pressure. Previous work in the animal model of ischemia reperfusion injury has shown that after an ischemic AKI event, renal sodium-handling is impaired and predisposes to salt-sensitive hypertension.⁴⁹ Hsu et al⁵⁰ evaluated the association between hospitalized AKI and blood pressure elevation in the 2 years following hospital discharge, in previously normotensive adults. Using carefully-matched controls, the authors reported that AKI survivors were more likely to have blood pressure elevation (>140/90 mmHg) over the follow-up period than patients without AKI (46.1% versus 41.2%; $P<0.001$). After multivariable adjustment, AKI was associated with a 22% increased odds for elevated blood pressure in the 2-year follow-up period. This risk also increased in a graded manner with increasing AKI severity, with Stage 2 and 3 AKI conferring odds ratios of 1.45 and 1.82, highlighting blood pressure as a potentially modifiable risk factor in the post-AKI period.

Mortality

Numerous studies have reported the association between AKI and both in-hospital and post-discharge mortality. In this review, we will limit the discussion to a few key studies that evaluated post-discharge mortality (Table 3). Lo et al¹³ reported that patients with baseline eGFR $<45\text{ mL/min/1.73m}^2$ and dialysis-requiring AKI had a 2-fold increased risk of death compared to matched patients not experiencing AKI. An association between less severe AKI and mortality has also been demonstrated. In the previously mentioned study by Ishani et al³² in the cardiac surgery setting, 3-month mortality risk increased in step-wise fashion with magnitude of post-operative creatinine increase (HRs 1.4-5.0), compared with patients who had no postoperative creatinine increase.

In a recent systematic review by Susantitaphong et al² of 106 studies using a KDIGO-equivalent definition of AKI, the pooled AKI-associated all-cause mortality (in-hospital and post-discharge) was 22.4%, with rates of 23.3% in adults and 13.8% in children. Of the 10 studies with follow-up duration of at least 6 months that included a non-AKI comparator group, the pooled unadjusted odds ratio (OR) for mortality in those experiencing AKI was 2.7, compared to patients without AKI.

Whether an AKI episode hastens death or merely serves as a surrogate marker of illness severity in patients already at increased risk of death is unclear, but studies have consistently shown that patients experiencing AKI are at higher risk of subsequent mortality than their counterparts without AKI. The ongoing Prevention of Serious Adverse Events following Angiography (PRESERVE) trial by Weisbord et al⁵¹ could help clarify this issue. In this study, patients with CKD are randomized to therapy aimed at preventing contrast-induced acute kidney injury (CI-AKI) or placebo, and clinical outcomes including 90-day and 1-year mortality are ascertained. If differences in mortality rates between groups are observed,

mediated by reduction in CI-AKI from the intervention, this may help to inform whether AKI is causal in, or simply a marker for, future mortality risk.

Summary

In summary, recent research indicates that AKI is not a ‘self-limited’ disease process, but rather a potential pathway to CKD, CVD, and future mortality. With an expanding population of AKI survivors at risk for these outcomes, it is imperative that optimal care practices for AKI survivors be developed to prevent these long-term consequences. Early nephrology follow-up after hospitalization with severe AKI has been associated with improved survival,⁵² though the processes driving this potential benefit are not clear. In the absence of routinely effective therapies to treat AKI, improving outcomes will require further work to identify high-risk patients who might benefit from improved surveillance, and to identify and evaluate interventions targeting modifiable risk factors that reduce the long-term consequences of AKI.

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Clinical Summary

- The number of AKI survivors is increasing rapidly due to the combined effects of population growth, a rising incidence of AKI, and improved short-term survival.
- AKI is associated with subsequent elevation in blood pressure, cardiovascular events, incident and progressive CKD, ESRD, and mortality.
- Optimal care for AKI survivors is not well-defined, and will require understanding the long-term implications of AKI, identifying patients at highest risk for these outcomes, and targeting modifiable risk factors for intervention.

Figure 1.

Delayed consequences of acute kidney injury.

Acute kidney injury (AKI) is associated with delayed consequences including: 1) elevated blood pressure (top), potentially through impaired-sodium handling and enhanced pressor response after AKI; 2) recurrent AKI (left), through physiologic derangements following an index AKI event that lower the threshold for subsequent injury; 3) incident or progressive CKD (bottom), through mechanisms that lead to tubulointerstitial fibrosis and progressive nephron loss; and 4) cardiovascular events (right), through distant organ dysfunction, with potential contributions from elevated blood pressure and CKD.

ESRD denotes end-stage renal disease.

Figure 2.

Risk factors for recurrent acute kidney injury.

Forest plot depicting the adjusted hazard ratios (aHRs) of risk factors for recurrent AKI using a Cox proportional hazards model. Confidence intervals that do not cross 1 denote statistical significance. Reprinted with permission.⁴⁰

Table 1

AKI and Development of Incident CKD

Author	N	Clinical Setting / Patient Characteristics	AKI Definition	Comparator Group	Follow-up (mean or median months)	Rate per 100 person-years	Hazard Ratio
Lo et al ¹³	3773	Hospitalized, GFR >45	Dialysis	GFR >45 without AKI	NA ^a	47.9	28.1
Amdur et al ⁵³	113,272	Hospitalized	Administrative codes for AKI or ATN	MI or pneumonia	75	NR	4.03-6.64 ^b
Ishani et al ³²	29,388	Cardiac surgery	Class I: 1-24%; Class II: 25-49%; Class III: 50-99%; Class IV: 100%	Cardiac surgery, no creatinine increase	61.2	NR	1.4-2.3 ^c
Bucaloiu et al ³³	5262	Hospitalized, GFR >60	SCr increase 50%	No AKI	40	2.81	1.91

Abbreviations: AKI, Acute Kidney injury; ATN, acute tubular necrosis; CKD, chronic kidney disease; GFR, glomerular filtration rate; MI, myocardial infarction; NA, not applicable; NR, not reported.

CKD Definitions: Stage 4 CKD in Lo¹³ and Amdur,⁵³ reduction in GFR to <60mL/min/1.73m² in Ishani,³² and reduction in GFR to 59mL/min/1.73m² in Bucaloiu.³³

^aFollow-up reported as 10,344 person-years.

^bHazard Ratio (HR) 4.03 for AKI and 6.64 for ATN.

^cRange of HRs for incident CKD at 5 years were 1.4, 1.9, 2.3, and 2.3 for Class I, II, III, and IV creatinine increases.

Table 2

AKI and Progressive CKD or ESRD

Author	N	Clinical Setting / Patient Characteristics	AKI Definition	Comparator Group	Follow-up (mean or median months)	Rate per 100 person-years		Hazard Ratio/Odds Ratio/Relative Risk	
						CKD Progression	ESRD	CKD Progression	ESRD
Newsome et al ⁵⁴	87,094	MI	SCr increase 0.3-0.59; 0.6-3.0	MI, No increase in SCr	49.2	—	0.6-2.0 ^a	—	2.36 - 3.26 ^d
James et al ⁵⁵	11,249	Coronary Angiography	AKIN	Coronary angiography, no AKI	21.8	NR	NR	1.60-3.12 ^b	
Wald et al ⁵⁶	8855	ICU	Dialysis	ICU, no AKI, no dialysis	36	—	2.63	—	3.23
Lafrance et al ⁵⁶	6862	Hospitalized CKD	GFR decrease 25% and >5mL/min/1.73m ²	CKD without AKI	19.4	—	NR	—	2.33 ^c
Ishani et al ⁹	233,803	Hospitalized	Administrative codes	No AKI or CKD	24	—	2.45	—	13.0
Ishani et al ³²	29,388	Cardiac surgery	Class I: 1-24%; Class II: 25-49%; Class III: 50-99%; Class IV: 100%	Cardiac surgery, no creatinine increase	61.2	NR	—	1.5-2.4 ^d	—
Wald et al ⁵⁷	82,654	Hospitalized	Administrative codes	No AKI	24	—	1.78	—	2.70
Hsu et al ⁵⁸	39,805	Hospitalized, GFR <45	Dialysis	CKD without AKI	NR	—	NR	—	1.47 [*]

Abbreviations: AKI, Acute Kidney injury; AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; ESRD, end-stage renal disease; GFR, glomerular filtration rate; ICU, intensive care unit; MI, myocardial infarction; NR, not reported; SCr, serum creatinine.

^aRange of rates and Hazard Ratios (HRs) is for AKI defined by SCr increase 0.3-0.59 and 0.6-3.0.

^bOutcome was a composite of decline in eGFR >4mL/min/1.73m² or initiation of chronic dialysis. Results represent Odds Ratios (ORs). Range of ORs is for AKIN Stage I vs Stage II or III AKI.

^cResults reported as Relative Risk.

^dCKD progression was defined as change to a higher CKD Stage. Range of HRs for progressive CKD at 5 years were 1.5, 1.7, 1.7, and 2.4 for Class I, II, III, and IV creatinine increases.

^{*}Not statistically significant (95% Confidence Interval 0.95 to 2.28).

Table 3

AKI and Mortality

Author	N	Clinical Setting / Patient Characteristics	AKI definition	Comparator Group	Follow-up (mean or median months)	Rate per 100 person-years	Hazard Ratio/ Odds Ratio/ Relative Risk
Hsu et al ⁵⁸	39,805	Hospitalized, GFR <45	Dialysis	CKD without AKI	NR	NR	1.30 ^a
Lo et al ¹³	3773	Hospitalized, GFR >45	Dialysis	GFR >45 without AKI	NA ^b	NR	2.3
Newsome et al ⁵⁴	87,094	MI	SCr increase 0.3-0.59; 0.6-3.0	MI, No increase in SCr	49.2	19.4-27.5 ^c	1.26-1.39 ^c
Wald et al ³⁵	8855	ICU	Dialysis	No AKI or dialysis	36	10.1	0.95
Lafrance et al ⁵⁶	6862	CKD	GFR decrease 25% and >5mL/min/1.73m ²	CKD without AKI	19.4	NR	2.32 ^d
Ishani et al ⁹	233,803	Hospitalized	Administrative codes	No AKI or CKD	24	NR	2.48
Ishani et al ³²	29,388	Cardiac surgery	Class I: 1-24%; Class II: 25-49%; Class III: 50-99%; Class IV: 100%	Cardiac surgery without AKI	61.2	NR	1.02-1.78 ^e
Wald et al ⁵⁷	82,654	Hospitalized	Administrative codes	No AKI	24	15.34	1.10

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; ICU, intensive care unit; MI, myocardial infarction; SCr, serum creatinine.

^a Hazard Ratio (HR) represents composite outcome of death or ESRD.

^b Follow-up reported as 10,344 person-years.

^c Range of rates and HRs are for AKI defined by SCr increase 0.3-0.59 and 0.6-3.0.

^d Results reported as Relative Risk.

^e Range of HRs for mortality at 5 years were 1.02, 1.16, 1.38, and 1.78 for Class I, II, III, and IV creatinine increases.